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ORIGINAL RESEARCH ARTICLE

Assessment of Non-vitamin K Oral Anticoagulants Use in a Tertiary Care Center in the USA: A Chart Review of 909 Patients

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Abstract

Background Non-vitamin K oral anticoagulants (NOACs) have emerged as an attractive alternative to vitamin K antagonists for various thromboembolic indications. However, prescribed NOAC doses are often inconsistent with drug labeling and prescribers might not consider the potential risks associated with concomitant use of other drugs, which can compromise NOACs' safety and effectiveness.

Methods A retrospective chart review was conducted in a tertiary care center in USA over a 4-month period. We studied patients whose home medications included NOACs and assessed the appropriateness as per drug labeling, taking into consideration relevant clinical factors and concomitant drug intake.

Results A total of 909 patients with a mean age of 70.6 ± 13.1 years, out of which 51.6% were males, were included. The majority of patients received NOACs for stroke prevention in atrial fibrillation (AF) (70.5%), or deep venous thrombosis/pulmonary embolism (DVT/PE) treatment (13.5%). The most common drug prescribed was apixaban (57.8%) followed by rivaroxaban (34.0%), and less frequently dabigatran (7.7%). Inappropriate dosing was significantly more frequent among older patients, those taking NOACs for AF, those taking a higher number of home medications, and those with a lower creatinine clearance. Seven hundred and six patients (77.67%) had at least one drug-NOAC interaction, out of which 515 were rated major interactions. Antiplatelets, amiodarone, non-steroidal anti-inflammatory medications, and calcium channel blockers were the most commonly interacting drugs.

Conclusion A significant number of patients received NOACs at doses inconsistent with the package labeling or had clinically significant drug–drug interactions with NOACs. Efforts are warranted to improve appropriate dosing and avoid significant drug interactions.

Key Points

Non–vitamin K oral anticoagulants (NOACs) have a high risk of causing significant patient harm or death if they are used inappropriately.

Prescribed NOAC doses are often inconsistent with drug labeling.

NOAC–drug interactions are common and can compromise safety and efficacy of NOACs.

NOACs need to be dosed appropriately and the patient followed regularly for changes in kidney function and drug–NOAC interactions.

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1 Introduction

Non-vitamin K oral anticoagulants (NOACs) have emerged as an alternative to vitamin K antagonists for various thromboembolic indications, including the prevention of stroke in patients with nonvalvular atrial fibrillation (AF), venous thromboembolism (VTE) prophylaxis in surgical patients, deep venous thrombosis (DVT), pulmonary embolism (PE), and the prevention of recurrent DVT and PE. NOACs exert their pharmacological effect by directly targeting the enzymatic activity of thrombin (dabigatran) or factor Xa (apixaban, rivaroxaban, and edoxaban) and are generally administered at fixed doses. They have several advantages over vitamin K antagonists, including more predictable pharmacokinetic and pharmacodynamic profiles, a rapid onset and offset of action, no need for laboratory monitoring, fewer drug and food interactions, and equal or superior efficacy and safety, including lower rate of intracranial hemorrhage [1, 2].

Patients prescribed NOACs need to be dosed appropriately at initiation and then followed regularly. Patients' relevant clinical factors, including indication, renal function, age, weight, comorbidities, and drug–drug interactions should be taken into consideration when prescribing NOACs. Clearance of NOACs is partially dependent on renal function, necessitating dose adjustment or drug discontinuation in patients with varying levels of kidney dysfunction. P-glycoprotein (P-gp) efflux transporter and cytochrome P450 (CYP450) enzyme complexes are the main interaction mechanisms of NOACs with other medications, with dose adjustment recommended in the setting of selected concomitant medications [3].

The use of NOACs is expected to continue to increase as clinicians gain more experience and support with data from the real world studies, which are usually consistent with that from clinical studies. Hence, it is important for clinicians to become familiar with key aspects of prescribing different NOACs and to choose a particular NOAC for a patient.

A recent study involving over 1500 patients with VTE showed a significant deviation from recommended NOAC doses or regimens (once vs twice daily) which resulted in overdosing or underdosing; consequently, higher rates of VTE recurrence and major bleeding were reported [4]. Another study investigated NOAC dosing patterns and associated outcomes in patients with AF; this study concluded that prescribed NOAC doses are often inconsistent with drug labeling, which can lead to worse safety outcomes [5]. Furthermore, a recent study found that among patients taking NOACs for AF, concurrent use of certain drugs that interact with NOACs was associated with increased risk for major bleeding compared with the use of NOACs alone [6]. This growing concern that actual prescribed NOAC doses are often inconsistent with drug labeling and that prescribers might not consider the potential risks associated with concomitant use of other drugs led us to conduct this study with the primary objective to assess the appropriate use of NOACs and factors associated with their inappropriate use.

2 Methods

A retrospective chart review was conducted in a tertiary care center, Huntsville Hospital, Huntsville, Alabama, USA. We studied patients whose home medications included apixaban, dabigatran, edoxaban, or rivaroxaban, between March 1 and June 30, 2017. We excluded patients if there was insufficient history or laboratory data to determine the appropriateness of NOAC use. We assessed the appropriateness of NOAC use as per drug labeling, taking into consideration patients' relevant clinical factors, including indication, renal and hepatic function, age, weight, comorbidities, and drug–drug interactions. The use of each NOAC was considered appropriate based on the product's package insert as well as Lexicomp Online® 2018 [7]. We calculated estimated creatinine clearance (CrCl) using the Cockcroft-Gault equation. Patients were considered to have a renal indication for dose reduction if receiving dabigatran for nonvalvular AF with a CrCl of < 30 mL/min, or rivaroxaban with a CrCl of < 50 mL/min, or edoxaban for nonvalvular AF or DVT/PE treatment with a CrCl of < 50 mL/min. Dose reduction for apixaban required two of the following three criteria: age ≥ 80 years, weight ≤ 60 kg, and serum creatinine level ≥ 1.5 mg/dL. Drug-drug interactions with NOACs, including risk rating and severity, were assessed using Lexicomp Online® 2018 [7]. The severity of a drug–drug interaction was considered "major" when the risk rating was X (avoid) or D (consider therapy modification). In addition, the severity was considered "moderate" or "minor" when the risk rating was C (monitor therapy) and B (no action needed), respectively.

Data collected included patient demographics, comorbidities, NOAC received, indication, dose, serum creatinine levels in the last 3–9 months (in a steady state and not during acute illness with acute kidney injury), liver function tests, and concomitant medications that can interact with NOACs (prescription and over-the-counter products). Ethical approval for this study was obtained from Huntsville Hospital's Institutional Review Committee.

All statistical analyses were done using the Statistical Package for the Social Sciences (SPSS) software. Chi square tests and odds ratios with 95% confidence intervals were performed to evaluate statistical associations between appropriate dosing and other parameters. The drug–drug interaction

with NOACs and appropriate use were calculated. Results were considered statistically significant when $p \leq 0.05$.

3 Results

During the study period 930 patients met the inclusion criteria, out of which 21 were excluded due to insufficient history or laboratory data. A total of 909 patients with a mean age of 70.6 ± 13.1 years, out which 51.6% were males, were included. The patients suffered from a high burden of comorbidities, with a mean of 7.3 ± 3.2, and a high frequency of polypharmacy, with a mean number of medications per patient of 12.2 ± 4.5. The majority of patients received NOACs for stroke prevention in AF (70.5%), followed by DVT/PE treatment (13.5%). The most common drug prescribed was apixaban (57.8%) followed by rivaroxaban (34.0%), and less frequently dabigatran (7.7%). Only five patients were prescribed edoxaban. Table 1 describes patient characteristics and

Table 1 Patient characteristics and indications for NOAC use

	Apixaban *N* = 525 (57.8%)	Rivaroxaban *N* = 309 (34.0%)	Dabigatran *N* = 70 (7.7%)	Edoxaban *N* = 5 (0.6%)	Total *N* = 909 (100%)
Age (years), mean (SD)	71.9 (12.3)	67.7 (14.4)	73.9 (9.9)	70.6 (13.6)	70.6 (13.1)
CrCl, mean (SD)	49.2 (25.6)	63.1 (32.4)	53.9 (24.3)	54.4 (30.1)	54.3 (28.9)
No. of comorbidities, mean (SD)	7.3 (3.1)	7.0 (3.3)	7.9 (3.1)	6.0 (0.7)	7.3 (3.2)
No. of home medications, mean (SD)	12.1 (4.4)	12.1 (4.7)	12.5 (4.4)	17.6 (6.5)	12.2 (4.5)
Sex, *n* (%)					
Male	266 (57.1)	156 (33.5)	44 (9.4)	3 (60)	469 (51.6)
Female	259 (59.1)	153 (34.9)	26 (5.9)	2 (40)	440 (48.4)
Indication, *n* (%)					
AF	385 (60.3)	186 (29.2)	67 (10.5)	3 (60)	641 (70.5)
DVT/PE treatment*	58 (47.9)	62 (51.2)	1 (0.8)	2 (40)	123 (13.5)
DVT/PE prophylaxis, recurrence#	32 (58.1)	43 (56.6)	1 (1.3)		76 (8.3)
Knee or hip replacement	50 (72.5)	18 (26.1)	1 (1.4)		69 (7.6)

AF atrial fibrillation, *CrCl* creatinine clearance, *DVT* deep venous thrombosis, *NOACs* non-vitamin K oral anticoagulants, *PE* pulmonary embolism, *SD* standard deviation

*Acute phase treatment

#Indefinite anticoagulation (reduced intensity dosing for prophylaxis against venous thromboembolism recurrence)

Table 2 Distribution of NOAC appropriate dosing by selected characteristics

	Appropriate dose *N* = 692 (76.1%)	Inappropriate dose *N* = 217 (23.9%)	Total *N* = 909	*P* value
Age (years), mean (SD)	69.7 (13.5)	73.2 (11.5)	70.6 (13.1)	< 0.05*
CrCl, mean (SD)	57.9 (29.7)	44.4 (23.8)	54.3 (28.9)	< 0.05*
No. of comorbidities, mean (SD)	7.2 (3.2)	7.5 (3.2)	7.3 (3.2)	0.102
No. of medications, mean (SD)	12.0 (4.8)	12.7 (4.6)	12.2 (4.5)	0.029*
Sex, *n* (%)				
Male	353 (75.3)	116 (24.7)	469	0.105
Female	314 (71.4)	126 (28.6)	440	
Indication, *n* (%)				
AF	447 (69.7)	194 (30.3)	641	0.001*
DVT/PE treatment	107 (87.0)	16 (13.0)	123	
DVT/PE prophylaxis, recurrence	76 (78.9)	16 (21.1)	92	
Knee or hip replacement	53 (76.8)	16 (23.2)	69	

AF atrial fibrillation, *CrCl* creatinine clearance, *DVT* deep venous thrombosis, *NOACs* non-vitamin K oral anticoagulants, *PE* pulmonary embolism, *SD* standard deviation

* indicates statistically significant

indications for NOAC use. Table 2 describes the assessment of whether the dosing of NOACs was appropriate. Data shows that out of 909 patients, 217 (23.9%) received doses inconsistent with the package labeling; 13.2% of patients received lower than recommended dosing, while 10.7% received higher than recommended dosing. The prevalence of inappropriate dosing was significantly more frequent among older patients, those taking NOACs for AF (30.3%) compared to those using it for DVT/PE treatment (13%), those taking a higher number of home medications, and those with a lower CrCl. There was no difference by patients' sex and mean number of comorbidities. Table 3 describes the reasons behind inappropriate dosing.

Thirteen patients (1.4%) with contraindications to any dose of NOACs due to severe renal or hepatic impairment and 126 patients (13.9%) with a body mass index (BMI) > 40 mg/m^2 and/or weight ≥ 120 kg received the drugs. Furthermore, one patient with antiphospholipid syndrome received rivaroxaban.

Seven hundred and six patients (77.67%) had at least one potential drug-NOAC interaction, (a total of 1248 drug interactions, out of which 515 (41.3%) were rated major interactions). Antiplatelets, amiodarone, non-steroidal anti-inflammatory medications, and calcium channel blockers were the most commonly involved drugs. Tables 4 and 5 describe NOAC-drug interactions.

4 Discussion

NOACs are considered high-risk medicines as they have a high risk of causing significant patient harm or death if they are used inappropriately. In this study, we aimed at assessing the appropriate use of NOACs and factors associated with their inappropriate use. The most common inappropriate use

Table 3 Inappropriate dosing of NOACs

	Apixaban	Rivaroxaban	Dabigatran	Edoxaban	Total, *n* (%)
Inappropriate dosing	127 (24.2%)	75 (24.3%)	14 (20%)	1 (20%)	217 (23.9%)
Underdosing	86	23	11	0	120 (13.2%)
Wrong frequency (once daily)	15	0	3	0	
Wrong dose for specific indication	9	12	0	0	
Unnecessary dose reduction for kidney dysfunction	0	11	8	0	
Other	- On hemodialysis and had unnecessary dose reduction: 8 - AF patients not meeting 2 out of 3 criteria for dose reduction: 54				
Overdosing	41	52	3	1	97 (10.7%)
Absence of adjustment in renal dysfunction	0	51	3	0	
Wrong dose for specific indication	13	1	0	0	
Drug-drug interaction necessitating dose reduction	19	0	0	1	
Other	- AF patients meeting 2 out of 3 criteria for dose reduction: 9				

AF atrial fibrillation, *NOACs* non-vitamin K oral anticoagulants

Table 4 Number of drug–drug interactions with NOACs

No. of interactions	Apixaban	Rivaroxaban	Dabigatran	Edoxaban	Total
0	119 (22.67%)	75 (24.27%)	9 (12.86%)	0 (0%)	203 (22.33%)
1	190 (36.19%)	104 (33.66%)	24 (34.29%)	4 (80%)	322 (35.42%)
2	150 (28.57%)	83 (26.86%)	23 (32.86%)	1 (20%)	257 (28.27%)
3	47 (8.95%)	33 (10.68%)	11 (15.71%)	0 (0%)	91 (10.01%)
4	19 (3.62%)	14 (4.53%)	3 (4.29%)	0 (0%)	36 (3.96%)
Mean ± SD	1.4 ± 1.0	1.38 ± 1.1	1.6 ± 1.0	1.2 ± 0.4	1.4 ± 1.1

NOACs non-vitamin K oral anticoagulants, *SD* standard deviation

Table 5 Drug interactions with NOACs

Severity	Risk rating (*N*)	Apixaban	Rivaroxaban	Dabigatran	Edoxaban
Major	X (11)	7 Phenytoin: 3 Primidone: 2 Enzalutamide: 1 Phenobarbital: 1	3 Phenytoin: 1 Carbamazepine: 2	1 Rifampin: 1	0
Major	D (485)	258 Antiplatelets: 221 (192 aspirin, 24 clopidogrel, 3 prasugrel, 2 ticagrelor) (16 received DAPT) NSAIDs: 32 Estrogen derivatives: 5	164 Antiplatelets: 113 (94 aspirin, 15 clopidogrel, 4 prasugrel) (13 received DAPT) NSAIDs: 39 Dronedarone: 5 Estrogen derivatives: 3 Clarithromycin: 2 Verapamil: 2	57 Antiplatelets: 32 (27 aspirin, 4 clopidogrel, 1 prasugrel) (7 received DAPT) Amiodarone: 15 Simvastatin: 4 Dronedarone: 3 NSAIDs: 2 Verapamil: 1	6 Antiplatelets: 2 (1 aspirin, 1 clopidogrel) Amiodarone: 2 Verapamil: 2
Moderate	C (489)	286 SSRIs/SNRIs: 166 Diltiazem: 60 Omega 3 fatty acids: 24 Dronedarone: 22 Vitamin E: 6 Fluconazole: 4 Verapamil: 2 Imatinib: 2	147 SSRIs/SNRIs: 113 Omega 3 fatty acids: 23 Vitamin E: 5 Deferasirox: 5 Cilostazol: 1	56 SSRIs/SNRIs: 21 PPIs: 17 Atorvastatin: 12 Omega 3 fatty acids: 4 Cilostazol: 2	0
Minor	B (244)	133 Amiodarone: 99 Ranolazine: 21 Propafenone: 8 Azithromycin: 4 Cyclosporine: 1	111 Amiodarone: 54 Diltiazem: 38 Ranolazine: 8 Azithromycin: 4 Fluconazole: 4 Propafenone: 3	0	0
Major		Combination of P-gp inhibitors with strong or moderate CYP3A4 inhibitors necessitating apixaban dose reduction by 50% or avoidance if dosage is 2.5 mg twice daily: 19 Amiodarone + diltiazem: 14 Propafenone + diltiazem: 2 Amiodarone + verapamil: 1 Amiodarone + imatinib: 1 Ranolazine + dronedarone: 1			
	Total	703	425	114	6

Risk rating: X: avoid, D: consider therapy modification, C: monitor therapy, B: no action needed

DAPT dual antiplatelet therapy, *NOACs* non-vitamin K oral anticoagulants, *NSAIDs* non-steroidal anti-inflammatory drugs, *P-gp* P-glycoprotein, *PPIs* proton pump inhibitors, *SNRIs* serotonin-norepinephrine reuptake inhibitors, *SSRIs* selective serotonin reuptake inhibitors

of NOACs identified in this study was inappropriate dosing (13.2% of patients received lower than recommended dosing, while 10.7% received higher than recommended dosing). Absence of dose reduction in patients with kidney disease and unnecessary dose reduction in patients with preserved kidney function were common in patients on rivaroxaban and dabigatran. As for apixaban, inappropriate dosing was mainly attributed to dose reduction when patients did not meet two of the three criteria for dose reduction (one criterion being serum creatinine level), failure to reduce dose due to drug–drug interaction, and giving the drug once daily instead of twice daily. Our results are consistent with previous studies conducted in the USA and other countries revealing some deviation from recommended NOAC doses or regimens [4, 5, 8, 9]. Using a large US administrative database, Yao et al. reported that among patients receiving NOACs with a renal indication for dose reduction, 43.0% received standard doses, while in patients with no renal indication for dose reduction, 13.3% received reduced doses [5]. Currently available NOACs depend to some extent on renal

function for clearance and may potentially accumulate in patients with renal dysfunction, leading to an increased risk of bleeding. On the other hand, unnecessary dose reduction in patients with preserved kidney function may result in sub-therapeutic levels of NOACs and, consequently, possible reduction in their effectiveness. Underdosing or overdosing of NOACs in the setting of renal dysfunction has been associated with increased risk of stroke, systemic embolism, VTE recurrence, and/or bleeding [4, 5]. In our study, we used the Cockcroft-Gault equation to estimate CrCl as recommended by the landmark stroke prevention trials and product monographs. The Modified Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulae do not correctly identify a significant proportion of patients who require NOAC dose adjustments [10].

The prevalence of inappropriate dosing was more frequent in patients with lower CrCl and in older patients, who are expected to have a lower CrCl due to age-related decline in renal function. This may explain the failure of some prescribers to adjust NOAC doses in this group of patients. Furthermore, patients who take a higher number of home medications have a higher prevalence of inappropriate dosing, which may be explained by an increased chance of drug-NOAC interaction necessitating, in certain cases, dose reduction of NOACs.

Approximately one out of every ten patients included in the study had either a BMI of > 40 kg/m^2 and/or a weight of ≥ 120 kg. Because there are limited clinical efficacy and toxicity data available for obese individuals, the International Society of Hemostasis and Thrombosis recommends avoidance of NOACs in patients with a BMI of > 40 kg/m^2 or a weight of ≥ 120 kg. Available evidence suggests that increased weight leads to decreased drug exposures, reduced peak concentrations and shortened half-lives. Switching to a vitamin K antagonist is recommended in this group of patients. If NOACs are used in obese patients, it is suggested that prescribers check anti-Xa for apixaban, edoxaban, and rivaroxaban; ecarin time or dilute thrombin time with appropriate calibrators for dabigatran; or mass spectrometry drug level for any of the NOACs [11].

Vitamin K antagonists remain the preferred agents in patients with antiphospholipid syndrome who require anticoagulation as there are very few data on the efficacy of NOACs in these patients. Signorelli et al. reported failure of thrombotic prevention with rivaroxaban in a series of eight patients with antiphospholipid syndrome [12]. One patient with antiphospholipid syndrome received rivaroxaban in our study.

NOAC-drug interaction was a common finding in our study. About eight out of ten patients received at least one drug that can interact with NOACs, and 515 interactions were rated major in severity, which necessitates either avoidance of such drug combinations or therapy modification. This drug–drug interaction can compromise efficacy and safety of NOACs.

The most common and significant drug–drug interaction was the concomitant use of NOACs and antiplatelets (aspirin, clopidogrel, prasugrel, and ticagrelor), which can increase the risk of bleeding [risk rating D (consider therapy modification); severity: major] [1, 7]. This drug combination should be carefully balanced against the potential benefit in each clinical situation. The Canadian product monograph of apixaban, rivaroxaban, and dabigatran recommends avoiding the concomitant use of NOACs and prasugrel or ticagrelor [7]. Some patients received NOACs along with dual antiplatelet therapy, which further increases the risk of bleeding; patients with coexisting coronary artery disease and AF undergoing percutaneous coronary intervention (PCI) usually receive triple antithrombotic therapy. Large randomized controlled trials are needed to suggest the optimal duration and dose of antiplatelets and/or NOAC therapy in this category of patients.

Other drugs that increase the risk of bleeding when co-administered with NOACs include nonsteroidal anti-inflammatory drugs [risk rating D (consider therapy modification); severity: major] and selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) [risk rating C (monitor therapy); severity: moderate] as they exhibit antiplatelet properties [7]. One-third of the studied patients received SSRIs/SNRIs in our study.

P-gp transporter and CYP450 enzymes are the main pathways where the most drug–drug interactions with NOACs occur. The most commonly seen drug–drug interactions related to these pathways involve amiodarone, dronedarone, diltiazem, verapamil, and ranolazine. These drugs (except ranolazine) are commonly used in patients with AF/flutter, the most common indication for NOAC use in our study, to control rate or rhythm. The importance of drug–drug interactions with NOACs is underappreciated, and healthcare professionals need to be aware of such interactions. When NOACs are co-administered with other medications with potential major interaction, certain measures should be taken such as dose modification or even drug avoidance, while close monitoring is recommended when the severity is moderate in nature.

The patients studied were suffering from an average of seven comorbidities and received an average of 12 medications. Polypharmacy constitutes an important risk factor for adverse events resulting from drug–drug interaction [13–15]. While polypharmacy in itself is not a contraindication for the use of NOACs, special care needs to be taken when treating these vulnerable patients.

Our study has several limitations. This was a retrospective review conducted at only one medical center. Data were collected from patients' electronic records, with the

potential for missing information. Furthermore, very few patients received edoxaban and were not included in some of the analysis.

5 Conclusion

A significant number of patients received NOACs at doses inconsistent with the package labeling, which could potentially result in patient harm. Clinically significant drug–drug interactions with NOACs are common, and clinicians have to consider the consequences of such interactions before these agents are prescribed. Efforts are warranted to improve appropriate dosing and avoid significant drug interactions.

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Compliance with Ethical Standards

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